

REMARKS

Status of the Claims

Claims 6-9 are pending. Claims 6-9 are rejected. Claim 8 is amended. Claims 1-5 and 10-13 are cancelled.

No new matter has been added. Reconsideration of the pending claims is respectfully requested.

The 35 U.S.C. §103(a) rejections

Claims 6-9 are rejected under 35 U.S.C. §103(a) as being obvious by **Yan et al.** (*Circulation* 96(8): Suppl. P. 1605 (1997) in view of either **Corral-Debrinski et al.** (*Mutation Research*, 275:169-180, 1992, refer to as **Corral-Debrinski I**) or **Corral-Debrinski et al.** (*JAMA*, 266 (13):1812-1816, 1991, referred to as **Corral-Debrinski II**) or **Berlett et al.** (*Jour. of Biol. Chem.*, 272 (33):20313-20316, 1997). This rejection is respectfully traversed.

The Examiner states that **Yan** teaches an *in vivo* relationship between reactive oxygen species and mitochondrial DNA damage in atherosclerosis. Specifically, **Yan** teaches assaying normal and diseased human aortic tissues for mitochondrial DNA

damage using quantitative PCR, where the aortic tissues in samples with evidence of atherosclerosis contained a higher degree of mitochondrial DNA damage than in the normal tissues. **Corral-Debrinski I** teaches an association of mitochondrial DNA damage with coronary atherosclerotic heart disease, by sampling post-mortem cardiac tissue and estimating mitochondrial DNA damage in the form of DNA deletions, using PCR. **Corral-Debrinski I** also suggests oxidative phosphorylation dysfunction is related to decreased cellular ATP, mitochondrial damage and oxygen radical formation. **Corral-Debrinski II** teaches oxidative phosphorylation increases oxygen radical generation, damage to mtDNA and reduces adenosine triphosphate synthesis. Finally, **Berlett** teaches oxidatively modified forms of proteins accumulate during aging, oxidative stress. Therefore, the Examiner argues that it would be *prima facie* obvious to one of ordinary skill in the art to modify the teachings of **Yan** with the teachings of **Corral-Debrinski I**, **Corral-Debrinski II** and **Berlett**. Applicants respectfully disagree.

Applicant respectfully argues that the teachings and suggestions of the cited references do not contain all the claim elements of the present invention, which is necessary to establish a *prima facie* case of obviousness under 35 U.S.C. §103(a) (M.P.E.P.

§2142). **Yan** is only an abstract that does not constitute an enabling disclosure sufficiently for the skilled person in the art to be able to carry its purported teachings. In addition, as pointed out by the Examiner, there is no teaching or suggestion in **Yan** that the measurement of mitochondrial DNA damage is correlated with measuring mitochondrial mRNA or protein production, or changes in mitochondrial oxidative phosphorylation or ATP production.

Corral-Debrinski I mainly teaches an association of mitochondrial DNA mutation with coronary atherosclerotic heart disease, but is not directed to disclose a method of measuring the amount of oxidative stress in an individual as claimed in the instant application. **Corral-Debrinski I** only provides a method of detection of permanent deletion mutations and does not provide any methodology for assessing the temporal equilibrium between incurred DNA damage and DNA repair that more accurately represents the status of oxidative stress. The methods of the instant invention detect temporal DNA damage as well as permanent mutations. Thus, the methods of the instant invention are more accurate and versatile. In addition, **Corral-Debrinski I** does not suggest the analysis of DNA from tissues other than cardiac tissue and does not even suggest the analysis of DNA from living patients.

Furthermore, there is no discussion of method to detect oxidative lesions in DNA in **Corral-Debrinski I**. In the absence of such suggestions, **Corral-Debrinski I** cannot render the instant invention obvious.

Corral-Debrinski II teaches the levels of nDNA and mtDNA oxidative phosphorylation (OXPHOS) transcripts level were increased in ischemic hearts compared to normal heart. However, the instant application discloses the mitochondrial DNA was more susceptible to acute doses of reactive oxygen species relative to the nuclear DNA, and was associated with a decrease (40%-60%) in mitochondrial encoded polypeptide OXPHOS transcripts (ND2 and Cytochrome b). Therefore, **Corral-Debrinski II** actually teaches away from the instant invention.

Berlett teaches accumulation of oxidized proteins during aging and some diseases. The oxidative modification of proteins mentioned in **Berlett** is nuclear DNA encoded protein, but not mitochondria proteins as measured and claimed herein. Therefore, one with ordinary skill in the art would not be motivated to improve the teachings of **Yan** by referring to the teachings of **Berlett** that has no description about mitochondrial function.

A *prima facie* case of obviousness also requires that the teaching or suggestion to combine the elements of the claimed invention with a reasonable expectation of success must be found in the prior art, and not based on Applicant's disclosure (M.P.E.P. §2142). Applicant respectfully submits that the cited references do not contain all of the limitations of claims 6-9, and that therefore the requisite motivation to combine the claimed elements with a reasonable expectation of success is not present. In order to be motivated to combine the elements of the claimed invention, one skilled in the art would require the teachings of the present application, so that a rejection for obviousness based on the references cited constitutes an impermissible hind-sight rejection (M.P.E.P. §2142). Also, the fact that references can be combined or modified does not render the combination obvious unless the prior art also suggests the desirability of the combination (M.P.E.P. §2143.01). Applicant respectfully submits that because **Corral-Debrinski I, Corral-Debrinski II** and **Berlett** teach a completely different criterion for measuring the amount of oxidative stress in an individual, such a desirability of combining the claimed elements is not present.

Accordingly, Applicant respectfully requests that the rejection of claims 6-9 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed February 05, 2004. Applicants submit that the pending claims are in condition for allowance. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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